

**PATENTS**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re application of: )  
                    **GRUBER et al** )  
Filed: **HEREWITH** )  
For: **ANTITHROMBOTIC THROMBIN VARIANTS**

**INFORMATION DISCLOSURE STATEMENT**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

Applicant hereby voluntarily discloses the reference listed on the attached Form PTO-1449 to the Assistant Commissioner for Patents. References (A-AA) were cited in a prior application relied upon by the above-identified application for an earlier filing date. The prior application relied upon is Application Serial No. 10/165,442, filed on June 7, 2002. It is specified in 37 CFR 1.98(d) that a "copy of any patent, publication or other information listed in an information disclosure statement is not required to be provided if it was previously cited by or submitted to the Office in a prior application, provided the prior application is properly identified in the statement and relied upon for an earlier filing date under 35 USC 120." Therefore please review the parent case for references (A-AA).

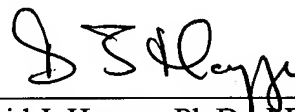
Applicant further reserves the right to establish the patentability of the claimed invention over any of the listed information should they be applied as references, and/or to prove that some of the cited information may not be prior art, and/or to prove that some of the cited information may not be enabling for the teachings they purport to offer. This statement further should not be construed as the representation that an exhaustive search has been made, or that the information cited herewith is material, or that there does not exist information more material to the examination of the present Application. The Examiner is specifically requested not to rely solely

on the information submitted herein. On the contrary, the Examiner is requested to conduct an independent and thorough review of the information, and to form independent opinions as to their significance.

It is respectfully requested that the Examiner initial and return copies of the enclosed PTO-1449 and to indicate in the official file wrapper of the above-identified patent application that each item of the cited information has been considered.

The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to account no. 09-0528.

Date: 10/31/2003

  
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**Docket No.: E056 1071.1**

<b>Form PTO-1449</b>				<b>Attorney Docket No.</b> E056 1071.1		<b>Serial No.</b>	
<b>INFORMATION DISCLOSURE CITATION</b>				<b>Applicants:</b> GRUBER et al			
				<b>Filing Date:</b> FILED HEREWITH		<b>Group Art Unit</b>	
<b>U.S. PATENT DOCUMENTS</b>							
Examiner Initials	Item	Document Number	Date	Name	Class	Subclass	Filing Date If Appropriate
<b>FOREIGN PATENT DOCUMENTS</b>							
		Document Number	Date	Country	Class	Subclass	Translation Yes No
<b>OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, etc.)</b>							
	A	Arosio, et al. - <i>Mutation of W215 Compromises Thrombin Cleavage of Fibrinogen, but Not of PAR-1 or Protein C</i> - Biochemistry 39, 8095-8101 (2000)					
	B	Bernard, et al. - <i>Efficacy and Safety of Recombinant Human Activated Protein C for Severe Sepsis</i> - N. Engl. J. Med. 344, 699-709 (2001)					
	C	Bonniec, et al. - <i>Glu-192 → Gln substitution in thrombin mimics the catalytic switch induced by thrombomodulin</i> - Proc. Natl. Acad. Sci. 88, 7371-7375 (1991)					
	D	Bouton, et al. - <i>Role of the thrombin insertion loop 144-155, Study of thrombin mutations W148G, K154E and a thrombin-based synthetic peptide</i> - Eur. J. Biochem. 229, 526-532 (1995)					
	E	Cantwell & Di Cera - <i>Rational Design of a Potent Anticoagulant Thrombin</i> - Journal of Biological Chemistry 275, 39827-39830 (2000)					
	F	Di Cera - <i>Anticoagulant Thrombins</i> - Trends in Cardiovascular Medicine 8, 340-350 (1998)					
	G	Gibbs, et al. - <i>Conversion of thrombin into an anticoagulant by protein engineering</i> - Nature 378, 413-416 (1995)					
	H	Gresele, et al. - <i>Activated Human Protein C Prevents Thrombin-induced Thromboembolism in Mice</i> - Journal for Clinical Investigation 101, 667-676 (1998)					
	I	Gruber, et al. - <i>The Thrombin Mutant W215A/E217A Shows Safe and Potent Anticoagulant and Antithrombotic Effects in Vivo</i> - Journal of Biological Chemistry 277, 27581-27584 (2002)					
	J	Gruber, et al. - <i>Direct Detection of Activated Protein C in Blood from Human Subjects</i> - Blood 79, 2340-2348 (1992)					
	K	Gruber, et al. - <i>Inhibition of Platelet-Dependent Thrombus Formation by Human Activated Protein C in a Primate Model</i> - Blood 73, 639-642 (1989)					
	L	Guinto, et al. - <i>Unexpected crucial role of residue 225 in serine proteases</i> - Proc. Natl. Acad. Sci. USA 96, 1852-1857 (1999)					
	M	Hanson, et al. - <i>Antithrombotic Effects of Thrombin-induced Activation of Endogenous Protein C in Primates</i> - Journal for Clinical Investigation 92, 2003-2012 (1993)					
<p>* EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP § 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to the applicant.</p>							
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<b>Form PTO-1449</b>				<b>Attorney Docket No.</b> E056 1071.1		<b>Serial No.</b>	
<b>INFORMATION DISCLOSURE CITATION</b>  <i>(Use several sheets if necessary)</i>				<b>Applicants:</b> GRUBER et al			
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<b>FOREIGN PATENT DOCUMENTS</b>							
		Document Number	Date	Country	Class	Subclass	Translation  Yes    No
<b>OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, etc.)</b>							
	N	Harker, et al. - <i>Experimental Arterial Thrombosis in Nonhuman Primates</i> - Circulation 83, IV-41-IV-55 (1991)					
	O	Ishii, et al. - <i>Thrombomodulin is Present in Human Plasma and Urine</i> - Journal for Clinical Investigation 76, 2178-2181 (1985)					
	P	Kogan, et al. - <i>Protein C Activator from the Venom of Aagkistrodon blomhoffi ussuriensis Retards Thrombus Formation in the Arterio-Venous Shunt in Rats</i> - Thrombosis Research 70, 385-393 (1993)					
	Q	Leung, et al. - <i>Dissociation of Thrombin's Substrate Interactions Using Site-Directed Mutagenesis</i> - Trends in Cardiovascular Medicine 10, 89-92 (2000)					
	R	Marder, et al. - <i>Plasmin Induces Local Thrombolysis without Causing Hemorrhage: A Comparison with Tissue Plasminogen Activator in the Rabbit</i> - Thrombosis Haemostasis 86, 739-745 (2001)					
	S	Martinoli, et al. - <i>Fast Functional Protein C Assay Using Protac, A Novel Protein C Activator</i> - Thrombosis Research 43, 253-264 (1986)					
	T	McBane, et al. - <i>Antithrombotic Action of Endogenous Porcine Protein C Activated with a Latent Porcine Thrombin Preparation</i> - Thrombosis Haemostasis 74, 879-885 (1995)					
	U	Richardson, et al. - <i>Enhancing protein C interaction with thrombin results in a clot-activated anticoagulant</i> - Nature 360, 261-264 (1992)					
	V	Sheehan, et al. - <i>Mutagenesis of Thrombin Selectively Modulates Inhibition by Serpins Heparin Cofactor II and Antithrombin III</i> - The Journal of Biological Chemistry 268, 3639-3645 (1993)					
	W	Takahashi, et al. - <i>Soluble Thrombomodulin Purified from Human Urine Exhibits a Potent Anticoagulant Effect In Vitro and In Vivo</i> - Thrombosis Haemostasis 73, 805-811 (1995)					
	X	Taylor, et al. - <i>Protein C Prevents the Coagulopathic and Lethal Effects of Escherichia coli Infusion in the Baboon</i> - Journal for Clinical Investigation 79, 918-925 (1987)					
	Y	Tsiang, et al. - <i>Protein Engineering Thrombin for Optimal Specificity and Potency of Anticoagulant Activity in Vivo</i> - Biochemistry 35, 16449-16457 (1996)					
	Z	Vindigni, et al. - <i>Release of Fibrinopeptides by the Slow and Fast Forms of Thrombin</i> - Biochemistry 35, 4417-4426 (1996)					
	AA	Wu, et al. - <i>Single amino acid substitutions dissociate fibrinogen-clotting and thrombomodulin-binding activities of human thrombin</i> - Proc. Natl. Acad. Sci. 88, 6775-6779 (1991)					
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